Attorney Docket No. 9310-151 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Sillekens et al.
Application No.: 10/559,949
Filing Date: December 22, 2006
Confirmation No.: 1079
Group Art Unit: 1637
Examiner: Joyce Tung
For: **NUCLEIC ACID SEQUENCES THAT CAN BE USED AS PRIMERS AND PROBES IN THE AMPLIFICATION AND DETECTION OR SARS CORONAVIRUS**

November 4, 2010

Mail Stop RCE
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE

Sir:

This is responsive to the final Office Action mailed July 6, 2010 (hereinafter "the Action") regarding the above-referenced patent application. A Request for Continued Examination and a Petition for Extension of Time is included herewith. Please enter the following amendments and consider the following remarks.

IN THE CLAIMS

Please amend the claims as follows. The following listing of claims replaces all prior versions.

1. (Canceled).

2. (Currently amended) ~~The pair of oligonucleotides according to claim 1,~~ A pair of oligonucleotides for amplification of a target sequence of the genome of SARS coronavirus, said pair consisting essentially of:

a first oligonucleotide being 10-50 nucleotides in length and comprising at least 10 contiguous nucleotides of a nucleotide sequence selected from the group consisting of:

SEQ ID NO:3: TCCACCAGGT GACCAGTTTA AACATCTT;

the complementary nucleotide sequence of SEQ ID NO:3;

SEQ ID NO:4: TAGTAGCTGT ACCGACTGGT TATGTT;

the complementary nucleotide sequence of SEQ ID NO:4;

~~SEQ ID 5: TACCTCTCCA GCTAGGATTT TCT~~

~~the complementary nucleotide sequence of SEQ ID NO:5;~~

SEQ ID NO:15: TCAGCCCCAG ATGGTACTTC T;

the complementary nucleotide sequence of SEQ ID NO:15;

~~SEQ ID 16: TAGGAACTGG CCCAGAAGCT TCACTT~~

~~the complementary nucleotide sequence of SEQ ID NO:16;~~

~~SEQ ID 24: TGCTCCAAGT GCCTCTGCAT TCTT~~

~~the complementary nucleotide sequence of SEQ ID NO:24;~~

SEQ ID NO:25: TTGGCATGGA AGTCACACCT T;

the complementary nucleotide sequence of SEQ ID NO:25;

~~SEQ ID 32: TGCCTATATG GAAGAGCCC~~

~~the complementary nucleotide sequence of SEQ ID NO:32;~~

~~SEQ ID 33: TCCCCATGTG ATTTTAATAG CTT~~

~~and the complementary nucleotide sequence of SEQ ID NO:33;~~

and

a second oligonucleotide being 10-50 nucleotides in length and comprising[[,]] at least 10 contiguous nucleotides of a nucleotide sequence selected from the group consisting of:

~~SEQ ID 6: ATGAATTACC AAGTCAATGG TTAC;~~

~~the complementary nucleotide sequence of SEQ ID NO:6;~~

SEQ ID NO:7: GAAGCTATTC GTCACGTTCG;

the complementary nucleotide sequence of SEQ ID NO:7;

SEQ ID NO:8: TGCGTGGATT GGCTTTGATG T;

the complementary nucleotide sequence of SEQ ID NO:8;

~~SEQ ID 18: AGGTTTACCC AATAATACTG CGT;~~

~~the complementary nucleotide sequence of SEQ ID NO:18;~~

SEQ ID NO:19: AGATTCCCTC GAGGCCAGGG CGT;

the complementary nucleotide sequence of SEQ ID NO:19;

~~SEQ ID 20: ATAGTGGTCC AGATGACCAA AT;~~

~~the complementary nucleotide sequence of SEQ ID NO:20;~~

~~SEQ ID 27: CCAAACTGTC ACTAAGAAAT CTGCT;~~

~~the complementary nucleotide sequence of SEQ ID NO:27;~~

~~SEQ ID 28: CTCAAGCATT TGGGAGACGT GGT;~~

~~the complementary nucleotide sequence of SEQ ID NO:28;~~

SEQ ID NO:29: CAGAACAAAC CCAAGGAAAT T; and

the complementary nucleotide sequence of SEQ ID NO:29~~;~~

~~SEQ ID 35: TACGATACAT AGTCTACTCT TGT;~~

~~the complementary nucleotide sequence of SEQ ID NO:35;~~

~~SEQ ID 36: TAACTAAACA GCACAAGTAG GT;~~

~~the complementary nucleotide sequence of SEQ ID NO:36;~~

~~SEQ ID 37: TAGCAATCTT TAATCAATGT;~~

~~and the complementary nucleotide sequence of SEQ ID NO:37~~.

3. (Canceled).

4. (Currently amended) ~~The pair of oligonucleotides according to claim 3,~~ A pair of oligonucleotides for amplification of a target sequence located within the replicase gene of the genome of SARS coronavirus, said pair consisting essentially of:

a first oligonucleotide being 10-50 nucleotides in length and comprising at least 10 contiguous nucleotides of a nucleotide sequence selected from the group consisting of:
SEQ ID NO:3: TCCACCAGGT GACCAGTTTA AACATCTT[[,]]; the complementary nucleotide sequence of SEQ ID NO:3[[,]];
SEQ ID NO:4: TAGTAGCTGT ACCGACTGGT TATGTT[[,]]; and the complementary nucleotide sequence of SEQ ID NO:4[[,]]
~~SEQ ID 5: TACCTCTCCA GCTAGGATTT TCT, and the complementary nucleotide sequence of SEQ ID NO:5~~;
and

a second oligonucleotide being 10-50 nucleotides in length and comprising at least 10 contiguous nucleotides of a nucleotide sequence selected from the group consisting of:
~~SEQ ID 6: ATGAATTACC AAGTCAATGG TTAC, the complementary nucleotide sequence of SEQ ID NO:6,~~
~~SED~~SEQ ID NO:7: GAAGCTATTC GTCACGTTCG[[,]]; the complementary nucleotide sequence of SEQ ID NO:7[[,]];
SEQ ID NO:8: TGCGTGGATT GGCTTTGATG T[[,]]; and the complementary nucleotide sequence of SEQ ID NO:8.

5. (Canceled).

6. (Currently amended) ~~The pair of oligonucleotides according to claim 5,~~A pair of oligonucleotides for amplification of a target sequence located within the gene encoding the nucleocapsid protein of the SARS coronavirus, said pair consisting essentially of:

a first oligonucleotide being 10-50 nucleotides in length and comprising at least 10 contiguous nucleotides of a nucleotide sequence selected from the group consisting of:
SEQ ID NO:15: TCAGCCCCAG ATGGTACTTC T; and

the complementary nucleotide sequence of SEQ ID NO:15;

~~SEQ ID 16: TAGGAACTGG CCCAGAAGCT TCACTT;~~

~~and the complementary nucleotide sequence of SEQ ID NO:16;~~

and

a second oligonucleotide being 10-50 nucleotides in length and comprising at least 10 contiguous nucleotides of a nucleotide sequence selected from the group consisting of:

~~SEQ ID 18: AGGTTTACCC AATAATACTG CGT;~~

~~the complementary nucleotide sequence of SEQ ID NO:18;~~

SEQ ID NO:19: AGATTCCCTC GAGGCCAGGG CGT; and

the complementary nucleotide sequence of SEQ ID NO:19~~;~~

~~SEQ ID 20: ATAGTGGTCC AGATGACCAA AT;~~

~~and the complementary nucleotide sequence of SEQ ID NO:20~~.

7. (Canceled).

8. (Currently amended) ~~The pair of oligonucleotides according to claim 7,~~ A pair of oligonucleotides for amplification of a target sequence located within the gene encoding the nucleocapsid protein of the SARS coronavirus, said pair consisting essentially of:

a first oligonucleotide being 10-50 nucleotides in length and comprising at least 10 contiguous nucleotides of a nucleotide sequence selected from the group consisting of:

~~SEQ ID 24: TGCTCCAA GTGCCTCTGC ATTCTT;~~

~~the complementary nucleotide sequence of SEQ ID NO:24;~~

SEQ ID NO:25: TTGGCATGGA AGTCACACCT T; and

the complementary nucleotide sequence of SEQ ID NO:25; and

a second oligonucleotide being 10-50 nucleotides in length and comprising at least 10 contiguous nucleotides of a nucleotide sequence selected from the group consisting of:

~~SEQ ID 27: CCAAACTGTC ACTAAGAAAT CTGCT;~~

~~the complementary nucleotide sequence of SEQ ID NO:27;~~

~~SEQ ID 28: CTCAAGCATT TGGGAGACGT GGT;~~

~~the complementary nucleotide sequence of SEQ ID NO:28;~~

SEQ ID NO:29 : CAGAACAAAC CCAAGGAAAT T;

and the complementary nucleotide sequence of SEQ ID NO:29.

9-10. (Canceled).

11. (Currently amended) The pair of oligonucleotides according to claim [[1]]2, wherein the first oligonucleotide is operably linked to a promoter sequence recognized by a DNA dependent RNA polymerase.

12. (Currently amended) The pair of oligonucleotides according to claim 11, wherein the first oligonucleotide consists essentially of the nucleotide sequence of:

SEQ ID NO:9: aattctaata cgactcacta tagggAAGAT GTTTAAACTG GTCACCTGGT GGA,

SEQ ID NO:10: aattctaata cgactcacta tagggAACAT AACCAGTCGG TACAGCTACT A,

~~SEQ ID 11: aattctaata cgactcacta tagggAGAAA ATCCTAGCTG GAGAGGTA,~~

SEQ ID NO:39: aattctaata cgactcacta tagggAGAAG TACCATCTGG GGCTGA, or

~~SEQ ID 40: aattctaata cgactcacta tagggAAGTG AAGCTTCTGG GCCAGTTCCT A,~~

~~SEQ ID 41: aattctaata cgactcacta tagggAAGAA TGCAGAGGCA CTTGGAGCA,~~

SEQ ID NO:42: aattctaata cgactcacta tagggAAGGT GTGACTTCCA TGCCAA,

~~SEQ ID 43: aattctaata cgactcacta tagggGGGCT CTTCCATATA GGCA, or~~

~~SEQ ID 44: aattctaata cgactcacta tagggAAGCT ATTAAAATCA CATGGGGA~~.

13. (Currently amended) The pair of oligonucleotides according to claim [[1]]2, wherein each oligonucleotide is 15-30 nucleotides in length and comprises at least 18 contiguous nucleotides.

14. (Canceled).

15. (Currently amended) ~~The oligonucleotide probe according to claim 14~~An oligonucleotide probe to detect an amplified target sequence located within the genome of SARS coronavirus, said target sequence amplified with the pair of oligonucleotides according to claim 2, wherein the probe comprises a molecular beacon selected from the group consisting of:
SEQ ID NO:13: 5'- [6-FAM]-ccatgggCTGTCATGCAACTAGAGATGCTGTcccatgg- [DabSyl]-3';
SEQ ID NO:45: 5'- [6-FAM]-cgcgatGTTCGTGCGTGGATTGGCTTatcgcg- [DabCyl]-3';
SEQ ID NO:22: 5'-[6-FAM]-ccatgggCTACTACCGAAGAGCTACCCGACGAcccatgg- [DabSyl]-3'; and
SEQ ID NO:30: 5'-[6-FAM]-ccatggACCAAGACCTAATCAGACAAccatgg- [DabSyl]-3'~~; and SEQ ID 47: 5'-[6-FAM]-ccatgcGCCACCACATTTTCATCGAgcatgg-[DabSyl]- 3'~~.

16. (Currently amended) A method for detecting SARS coronavirus nucleic acid in a sample, comprising:

(a) employing the sample in a nucleic acid amplification reaction under conditions whereby amplification of SARS coronavirus nucleic acid can occur; and

(b) detecting amplified SARS coronavirus nucleic acid in the sample using the pair of oligonucleotides of claim [[1]]2.

17. (Currently amended) A method for detecting SARS coronavirus nucleic acid in a sample, comprising:

(a) contacting the sample with the pair of oligonucleotides of claim [[1]]2 under conditions whereby amplification of SARS coronavirus nucleic acid can occur; and

(b) detecting amplified SARS coronavirus nucleic acid.

18. (Currently amended) The method according to claim 17, wherein detecting the amplified nucleic acid comprises[[:]] contacting the amplified SARS ~~eronavirus~~coronavirus nucleic acid with an oligonucleotide probe under conditions whereby hybridization can occur, said probe comprising the oligonucleotide probe of claim 15 ~~being 10-50 nucleotides in length and comprising at least 10 contiguous nucleotides of the nucleotide sequence of:~~

~~SEQ ID 12: GTTCGTGCGT GGATTGGCTT TGATGTAGAG GGCTGTCATG CAACTAGAGA TGCTGT, or its complementary sequence,~~

~~SEQ ID 21: GGCTACTACC GAAGAGCTAC CCGACGAGTT CGTGGTGGTG ACGGCAAAAT GAAAGAGCTC AGCCCCAGAT GGTACTTCTA TTACCTAGGA ACTGGCCCAG AAGCTTCACT TCCCTACGGC GCTAACAAAG AAGGCATCGT ATGGGTTGCA ACTGAGGGAG CCTTGAATAC ACCCAAAGAC CACATTGGCA CCCGCAATCC TAATAACAAT GCTGCCACCG TGCTACAACT TCCTCAAGGA ACAACATTGC CAAAAGGCTT CTACGCAGAG GGAAGCAGAG GCGGCAGTCA AGCCTCTTCT CGCTCCTCAT CACGTAGTCG CGGTAATTCA AGAAATTCAA CTCCTGGCAG CAGTAGGGGA AATTCTCCTG CTCGAATGGC TAGCGGAGGT GGTGAAACTG CCCTCGCGCT ATTGCTGCTA GACAGATTGA ACCAGCTTGA GAGCAAAGTT TCTGGTAAAG GCCAACAACA ACAAGGCCAA ACTGTCACTA AGAAATCTGC TGCTGAGGCA TCTAAAAAGC CTCGCCAAAA ACGTACTGCC ACAAAACAGT ACAACGTCAC TCAAGCATTT GGGAGACGTG GTCCAGAACA AACCCAAGGA AATTTCGGGG ACCAAGACCT AATCAGACAA, or its complementary sequence, or~~

~~SEQ ID 38: GCCACCACAT TTTCATCGAG GC, or its complementary sequence, wherein the probe further comprises a detectable label~~.

19. (Previously Presented) The method according to claim 17, wherein the nucleic acid amplification comprises a NASBA transcription based amplification technique, and the first oligonucleotide is operably linked to a promoter sequence recognized by a DNA dependent RNA polymerase.

20. (Currently amended) A test kit for the detection of SARS coronavirus in a sample, comprising:

the pair of oligonucleotides according to claim [[1]]2,

an oligonucleotide, for use as a probe, said probe comprising an oligonucleotide probe of claim 15~~comprising a nucleic acid sequence substantially complementary to at least part of an~~

~~amplified nucleic acid sequence and a detectable label, said probe being 10-50 nucleotides in length and comprising at least10 contiguous nucleotides of the nucleotide sequence of:~~

~~SEQ ID 12: GTTCGTGCGT GGATTGGCTT TGATGTAGAG GGCTGTCATG CAACTAGAGA TGCTGT, or its complementary sequence,~~

~~SEQ ID 21: GGCTACTACC GAAGAGCTAC CCGACGAGTT CGTGGTGGTG ACGGCAAAAT GAAAGAGCTC AGCCCCAGAT GGTACTTCTA TTACCTAGGA ACTGGCCCAG AAGCTTCACT TCCCTACGGC GCTAACAAAG AAGGCATCGT ATGGGTTGCA ACTGAGGGAG CCTTGAATAC ACCCAAAGAC CACATTGGCA CCCGCAATCC TAATAACAAT GCTGCCACCG TGCTACAACT TCCTCAAGGA ACAACATTGC CAAAAGGCTT CTACGCAGAG GGAAGCAGAG GCGGCAGTCA AGCCTCTTCT CGCTCCTCAT CACGTAGTCG CGGTAATTCA AGAAATTCAA CTCCTGGCAG CAGTAGGGGA AATTCTCCTG CTCGAATGGC TAGCGGAGGT GGTGAAACTG CCCTCGCGCT ATTGCTGCTA GACAGATTGA ACCAGCTTGA GAGCAAAGTT TCTGGTAAAG GCCAACAACA ACAAGGCCAA ACTGTCACTA AGAAATCTGC TGCTGAGGCA TCTAAAAAGC CTCGCCAAAA ACGTACTGCC ACAAAACAGT ACAACGTCAC TCAAGCATTT GGGAGACGTG GTCCAGAACA AACCCAAGGA AATTTCGGGG ACCAAGACCT AATCAGACAA, or its complementary sequence, or~~

~~SEQ ID 38: GCCACCACAT TTTCATCGAG GC, or its complementary sequence~~,

and

suitable amplification reagents.

21. (Previously Presented) The test kit according to claim 20, wherein the suitable amplification reagents enable a NASBA transcription based amplification technique.

22. (Currently amended) The pair of oligonucleotides according to claim [[1]]2, wherein each oligonucleotide is 18-26 nucleotides in length and comprises at least 20 contiguous nucleotides.

REMARKS

Claims 1-22 are pending in the application. Claims 1, 3, 5, 7, 9-10 and 14 are canceled herein without prejudice or disclaimer. Claims 2, 4, 6, 8, 11-13, 15-18 and 20 are amended herein for clarity and to more particularly define the invention. Support for these amendments is set forth in the language of the original claims and throughout the specification as set forth below. It is believed that no new matter is added by these amendments and their entry and consideration are respectfully requested. In light of these amendments and the following remarks, applicants respectfully request reconsideration of this application and allowance of the pending claims to issue.

Rejections under 35 U.S.C. §103(a)

As stated in the Examination Guidelines for Determining Obviousness, "the Supreme Court reaffirmed the familiar framework for determining obviousness as set forth in *Graham v. John Deere Co*...." (Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc*. Federal Register Vol. 72, No. 195, 57526-57535, 57526). Hence, and as long established under that framework, to establish a *prima facie* case of obviousness, three requirements must be satisfied. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some **suggestion or incentive that would have motivated** the skilled artisan to modify a reference or to combine references. *In re Oetiker,* 24 U.S.P.Q.2d 1443, 1446 (Fed. Cir. 1992); *In re Fine*, 837 F.2d at 1074; *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Second, the proposed modification or combination of the prior art must have a **reasonable expectation of success**, determined from the vantage point of the skilled artisan at the time the invention was made. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Third, the prior art reference or combination of references **must teach or suggest all of the limitations of the claims** . *See In re Wilson* 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (CCPA 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art"). Furthermore, as stated in *KSR Int'l Co. v. Teleflex In,* "[a] patent composed of several elements is not proved obvious merely by demonstrating that

each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc.*, 550 U. S. 1, 15 (2007).

Applicants respectfully submit that the pending claims are patentable over the cited references for at least the reasons that the cited references fail to teach or suggest all of the limitations of the claims nor do they provide the requisite suggestion or incentive that one of ordinary skill in the art would have to have had to combine these teachings in order to achieve the compositions and methods of the present invention exactly as claimed. Further, even if combined, the proposed modification/combination fails to provide a reasonable expectation of success in achieving the claimed invention. Thus, the Examiner has failed to make a *prima facie* case of obviousness.

A. Claims 1-4, 11-14, 16-18 and 22 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Laue (U.S. Patent No. 7,374,883) in view of Lowe et al. (Nucleic Acids Res. 18:1757-1761 (1990)). Specifically, the Office Action alleges that SEQ ID NO:1 of Laue comprises instant SEQ ID NO:1 and instant SEQ ID NO:2. The Office Action further alleges that one of ordinary skill in the art would have been motivated to construct a pair of oligonucleotides with instant SEQ ID NOs:1 and 2 for amplifying a target sequence of the genome of SARS coronavirus with a reasonable expectation of success because Laue discloses a method of detecting SARS with a pair of primers and a known sequence and Lowe et al. discloses a computer program for selecting primers for PCR from a known sequence. On this basis, the Office Action concludes that it would have been *prima facie* obvious to construct a pair of oligonucleotides from within the instant SEQ ID NOs:1 and 2 for amplifying a target sequence of the genome of SARS coronavirus as claimed. Applicants respectfully traverse this rejection.

Claims 1, 3 and 14 are canceled herein without prejudice or disclaimer, thereby mooting this rejection as it pertains to these claims.

Claim 2 is amended herein to recite a pair of oligonucleotides consisting essentially of a first oligonucleotide being 10-50 nucleotides in length and comprising at least 10 contiguous nucleotides of a nucleotide sequence selected from the group consisting of: SEQ ID NO:3, the complementary nucleotide sequence of SEQ ID NO:3, SEQ ID NO:4, the complementary nucleotide sequence of

SEQ ID NO:4, SEQ ID NO:5, the complementary nucleotide sequence of SEQ ID NO:5, SEQ ID NO:25 and the complementary nucleotide sequence of SEQ ID NO:25; and a second oligonucleotide being 10-50 nucleotides in length and comprising at least 10 contiguous nucleotides of a nucleotide sequence selected from the group consisting of: SEQ ID NO:7, the complementary nucleotide sequence of SEQ ID NO:7, SEQ ID NO:8, the complementary nucleotide sequence of SEQ ID NO:8, SEQ ID NO:19, the complementary nucleotide sequence of SEQ ID NO:19, SEQ ID NO:29, and the complementary nucleotide sequence of SEQ ID NO:29. Support for this amendment can be found at least, for example, in original claims 1 and 2.

Claim 4 as presented herein recites a pair of oligonucleotides for amplification of a target sequence located within the replicase gene of the genome of SARS coronavirus, said pair consisting essentially of a first oligonucleotide being 10-50 nucleotides in length and comprising at least 10 contiguous nucleotides of a nucleotide sequence selected from the group consisting of: SEQ ID NO:3, the complementary nucleotide sequence of SEQ ID NO:3, SEQ ID NO:4, and the complementary nucleotide sequence of SEQ ID NO:4; and a second oligonucleotide being 10-50 nucleotides in length and comprising at least 10 contiguous nucleotides of a nucleotide sequence selected from the group consisting of: SEQ ID NO:7, the complementary nucleotide sequence of SEQ ID NO:7, SEQ ID NO:8, and the complementary nucleotide sequence of SEQ ID NO:8. Support for this amendment can be found at least, for example, in original claims 3 and 4.

Claim 8 as presented herein recites a pair of oligonucleotides for amplification of a target sequence located within the gene encoding the nucleocapsid protein of the SARS coronavirus, said pair consisting essentially of a first oligonucleotide being 10-50 nucleotides in length and comprising at least 10 contiguous nucleotides of a nucleotide sequence selected from the group consisting of: SEQ ID NO:25, and the complementary nucleotide sequence of SEQ ID NO:25; and a second oligonucleotide being 10-50 nucleotides in length and comprising at least 10 contiguous nucleotides of a nucleotide sequence selected from the group consisting of: SEQ ID NO:29, and the complementary nucleotide sequence of SEQ ID NO:29. Support for this amendment can be found at least, for example, in original claims 7 and 8.

Claim 12 as presented herein recites a pair of oligonucleotides wherein the first oligonucleotide consists essentially of the nucleotide sequence of: SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:39, or SEQ ID NO:42. Claim 15 recites an oligonucleotide probe, wherein the probe comprises a molecular beacon selected from the group consisting of: SEQ ID NO:13, SEQ ID NO:45, SEQ ID NO:22, and SEQ ID NO:30. Support for this amendment can be found at least, for example, in original claims 1, 2, 11, and 12.

The genome of the SARS coronavirus is approximately 29,750 bases in length. Laue discloses a 300 nucleotide sequence of the SARS genome and from this sequence provides particular primer pairs for detection of SARS using PCR. However, Laue fails to teach or suggest the specific primer pairs of the presently claimed invention. Further, the secondary reference, Lowe et al., fails to remedy the deficiencies of Laue.

Lowe et al. provides a program for finding, in a selected sequence, those sequences that fulfill the criteria designated by the user for the desired primers. The Office Action asserts that Lowe et al. would allow for selection of primers for PCR from a known sequence. However, the Lowe et al. program is not sufficient for identifying useful SARS coronavirus primers as defined by the claimed invention, for at least the reason that after selecting the target sequence, the ordinary skilled person using the program must still single out and select the presently claimed pairs of primers from the large number of possible primers produced by the program. As noted above, the SARS coronavirus genome is over 29,750 bases in length; thus, the potential number of different primers and primer pair combinations would be exceedingly large. Even inputting the 300 bases of the nucleotide sequence of Laue would result in an extremely large population of primers, with no direction provided for how to select among the primers or how to select for specific primer pairs. Nothing in the cited art teaches or suggests or provides any direction for selecting the specific primer pairs of the present invention.

Further, data in the present specification show that the claimed pairs of oligonucleotides have greater sensitivity and/or better kinetics when compared to other primer pair combinations developed from SARS. For example, Figs. 1-5 and 7-11, and pages 33-34 show and discuss the superior kinetics and the lower time to positivity for SARS-COV-Rep primer pair P1.1/P2.2 (SEQ ID NO:10 (SEQ ID NO:4)/SEQ ID NO:7) and P1.3/P2.3 (SEQ ID NO:9 (SEQ ID NO:3)/SEQ ID

NO:8) as compared to other primer pairs for SARS-COV Rep. Figs. 13-16, 17-20 and 29-34, and page 44, lines 27-32 and page 45, lines 6-14, show and discuss the SARS-COV-N (region 1) primer pair P1.1/P2.2 (SEQ ID NO:15 (SEQ ID NO:39)/SEQ ID NO:19) as the most favorable primer pair due to it being most efficient at detecting the nucleic acid extract resulting from 1 genomic equivalent (geq). Finally, the increased sensitivity of the SARS-COV-N (region 2) primer pair P1.4/P2.6 (SEQ ID NO:42 (SEQ ID NO:25)/SEQ ID NO:29) is shown in Figs. 35-40 and discussed in the paragraph bridging pages 47-48.

Thus, it is clear that not all primers and primer pairs prepared for amplification and detection of SARS are functionally equivalent to the claimed primer pairs. These results are surprising and could not have been predicted nor could any computer program such as that of Lowe et al. have selected these particular primer pairs out of the 29,750 bp nucleotide sequence of the SARS genome or even the 300 bp nucleotide sequence of Laue.

Thus, the cited references fail to teach or suggest the specific primers of the presently claimed invention, they fail to provide the motivation to combine the cited references in order to achieve the presently claimed invention and even if combined the cited references fail to provide a reasonable expectation of success in achieving the presently claimed invention.

Accordingly, applicants submit that the pending claims are patentable over Laue in view of Lowe et al., and respectfully request the withdrawal of this rejection.

B. Claims 5 and 6 stand rejected under 35 U.S.C. §103 as allegedly being unpatentable over Ahn et al. (Korean Patent Application No. 10-2003-0034331) in view of Lowe et al. and Laue. Specifically, the Office Action states that Ahn et al. discloses a nucleic acid sequence from SARS virus which comprises instant SEQ ID NOs:14 and 17. The Office Action further states that one of ordinary skill in the art would have been motivated to construct a pair of oligonucleotides within instant SEQ ID NOs:14 and 17 for amplifying a target sequence encoding the nucleocapsid protein of SARS coronavirus with a reasonable expectation of success because Ahn et al. discloses a known nucleic acid sequence, Laue discloses a method of detecting SARS with a pair of primers and Lowe et al. discloses a computer program for selecting oligonucleotide primers for PCR from a known sequence. On this basis, the Office Action concludes that it would have been *prima facie* obvious to

construct a pair of oligonucleotides from within the instant SEQ ID NOs:14 and 17 for amplifying a target sequence of the genome of SARS coronavirus. Applicants respectfully traverse this rejection.

Claim 5 is canceled herein without prejudice or disclaimer, thereby mooting this as it pertains to this claim.

Claim 6 as presented herein recites a pair of oligonucleotides for amplification of a target sequence located within the gene encoding the nucleocapsid protein of the SARS coronavirus, said pair consisting essentially of a first oligonucleotide being 10-50 nucleotides in length and comprising at least 10 contiguous nucleotides of a nucleotide sequence selected from the group consisting of: SEQ ID NO:15 and the complementary nucleotide sequence of SEQ ID NO:15; and a second oligonucleotide being 10-50 nucleotides in length and comprising at least 10 contiguous nucleotides of a nucleotide sequence selected from the group consisting of: SEQ ID NO:19 and the complementary nucleotide sequence of SEQ ID NO:19. Support for this amendment can be found at least, for example, in original claims 5 and 6.

As set forth above, the genome of the SARS coronavirus is approximately 29,750 bases in length. Ahn et al. discloses a 520 nucleotide sequence of the SARS genome. However, Ahn et al. fails to teach or suggest the specific primer pairs as claimed in the present invention, i.e., the nucleotide sequence of SEQ ID NO:15 and the nucleotide sequence of SEQ ID NO:19. Further, Lowe et al. and Laue fail to remedy the deficiencies of Ahn et al.

As discussed above, Lowe et al. provides a program for finding, in a pre-selected sequence, those sequences that fulfill the criteria designated by the user for the desired primers. The Office Action asserts that Lowe et al. would allow for selection of primers for PCR from a known sequence. However, the Lowe et al. program is not sufficient for identifying useful SARS coronavirus primers, as defined by the claimed invention, for at least the reason that after selecting the target sequence, the ordinary skilled person using the program must still single out and select the presently claimed pairs of primers from the vast number of possible primers produced by the program. As noted above, the SARS coronavirus genome is over 29,750 bases in length; thus, the potential number of different primers and primer pair combinations would be exceedingly large. Even inputting the 520 bases of the nucleotide sequence of Ahn et al. would result in an extremely large population of primers, with no direction provided in how to select among the primers or how

to select for any specific primer pairs. Nothing in the cited art teaches or suggests or provides any guidance in selecting the specific primer pairs of the present invention.

Laue discloses a method of detecting SARS with a pair of primers that are not the primers of the present invention. Thus, similar to Ahn et al., Laue fails to teach or suggest the specific primer pairs of the presently claimed invention.

Furthermore, as discussed above, data presented in the originally filed specification show that the claimed pair of oligonucleotides have greater sensitivity and/or better kinetics when compared to other primer pairs developed from SARS. The primer pair of SEQ ID NO:15 and SEQ ID NO:19 corresponds to the SARS-COV N (region 1) primer pair P1.1/P2.2. The comparative data for this primer pair can be found in the specification, for example, in Figs. 13-16, 17-20 and 29-34, and on page 44, lines 27-32 and on page 45, lines 6-14. SARS-COV-N (region 1) primer pair P1.1/P2.2 (SEQ ID NO:15 (39)/SEQ ID NO:19) is determined to be the most favorable primer pair due to it being the most efficient at detecting the nucleic acid extract resulting from 1 genomic equivalent (geq).

Thus, it is clear that not all primers and primer pairs prepared for amplification and detection of SARS are functionally equivalent to the claimed primer pairs. These results are surprising and could not have been predicted nor could any computer program such as that of Lowe et al. have selected these particular primer pairs out of the 29,750 bp nucleotide sequence of the SARS genome or even the 520 bp nucleotide sequence of Ahn et al.

Thus, the cited references fail to teach or suggest or provide any direction to produce the specific primers of the presently claimed invention, they fail to provide the motivation to combine the cited references in order to achieve the presently claimed invention and even if combined the cited references fail to provide a reasonable expectation of success in achieving the presently claimed invention.

Accordingly, applicants submit that pending claim 6 is patentable over Ahn et al. in view of Lowe et al. and Laue and respectfully request the withdrawal of this rejection.

C. Claims 7-10 stand rejected under 35 U.S.C. §103 as allegedly being unpatentable over Briese et al. (U.S. Patent Publication No 20040265796) in view of Lowe et al. Specifically, the Office Action alleges that SEQ ID NO:1 of Briese et al. comprises instant SEQ ID NOs:23, 26 and 34 and that Figure 1 of Briese et al. comprises instant SEQ ID NO:31 of the presently claimed invention. The Office Action further states that one of ordinary skill in the art would have been motivated to construct a pair of oligonucleotides within the gene encoding the nucleocapsid protein of the genome of SARS coronavirus with a reasonable expectation of success because Briese et al. discloses an assay for detecting SARS with a pair of primers from a known sequence and Lowe et al. discloses a computer program for selecting oligonucleotide primers for PCR from a known sequence. On this basis, the Examiner concludes that it would have been *prima facie* obvious to construct a pair of oligonucleotides within SEQ ID NOs:23, 26, 31, and 34 for amplifying a target sequence located within the gene encoding the nucleocapsid protein of the genome of SARS coronavirus. Applicants respectfully traverse this rejection.

Claims 7, 9 and 10 are canceled herein without prejudice or disclaimer, thereby mooting this rejection at least as it pertains to these claims.

Claim 8 as presented herein recites a pair of oligonucleotides for amplification of a target sequence located within the gene encoding the nucleocapsid protein of the SARS coronavirus, said pair consisting essentially of: a first oligonucleotide being 10-50 nucleotides in length and comprising at least 10 contiguous nucleotides of a nucleotide sequence selected from the group consisting of: SEQ ID NO:25 and the complementary nucleotide sequence of SEQ ID NO:25; and a second oligonucleotide being 10-50 nucleotides in length and comprising at least 10 contiguous nucleotides of a nucleotide sequence selected from the group consisting of: SEQ ID NO:29 and the complementary nucleotide sequence of SEQ ID NO:29.

SEQ ID NO:1 of Briese et al. is a sequence of 1136 nucleotides from the SARS genome. Figure 1 of Briese et al. discloses the SARS-associated coronavirus genome, which is over 29,750 bases in length. Briese et al. fails to identify or suggest the specific primers and primer pairs as claimed in the present invention, i.e., SEQ ID NO:25, and SEQ ID NO:29 from among the 1136 nucleotides disclosed in SEQ ID NO:1 of Briese et al. or from the entire genome of the SARS-

associated coronavirus as disclosed in Figure 1 of Briese et al. Further, the secondary reference, Lowe et al., fails to remedy the deficiencies of Briese et al.

As discussed above, Lowe et al. provides a program for finding, in a pre-selected sequence, those sequences that fulfill the criteria designated by the user for the desired primers. The Office Action asserts that Lowe et al. would allow for selection of primers for PCR from a known sequence. However, the Lowe et al. program is not sufficient for identifying useful SARS coronavirus primers, as defined by the claimed invention, for at least the reason that after selecting the target sequence, the ordinary skilled person using the program must still single out and select the presently claimed pairs of primers from the vast number of possible primers produced by the program. Inputting the 1136 bases of the nucleotide sequence of SEQ ID NO:1 of Briese et al. or the entire genome of the SARS coronavirus as presented in Figure 1 of Briese et al. would result in an exceedingly large population of primers, with no direction provided in Briese et al. as to how to select among the primers or for specific primer pairs.

Furthermore, as discussed above, data presented in the specification as originally filed show that the claimed pair of oligonucleotides have greater sensitivity and/or better kinetics when compared to other primer pairs developed from SARS. The primer pair, SEQ ID NO:25 and SEQ ID NO:29, correspond to the SARS-COV N (region 2) primer pair P1.4/P2.6. The data for this primer pair can be found in the specification, for example, in Figs. 35-40, and the paragraph bridging pages 47-48. The SARS-COV-N (region 2) primer pair P1.4/P2.6 (SEQ ID NO:25/SEQ ID NO:29) is shown to have increased sensitivity and this sensitivity was not shown for the P2.6 primer when in combination with other primers such as the P1.3 primer (SEQ ID NO:41).

As discussed previously, it is clear that not all primers and primer pairs prepared for amplification and detection of SARS are functionally equivalent to the claimed primer pairs. These results are surprising and could not have been predicted nor could any computer program such as that of Lowe et al. have selected these particular primer pairs out of the 29,750 bp nucleotide sequence of the SARS genome or even the 1136 bp nucleotide sequence of Briese et al..

Thus, the cited references fail to teach or suggest or provide any direction to produce the specific primers of the presently claimed invention, they fail to provide the motivation to combine the cited references in order to achieve the presently claimed invention and even if combined the

cited references fail to provide a reasonable expectation of success in achieving the presently claimed invention.

Accordingly, applicants submit that pending claim 8 is patentable over Briese et al. in view of Lowe et al. and respectfully request the withdrawal of this rejection.

D. Claim 15 stands rejected under 35 U.S.C. §103 as allegedly being unpatentable over Laue in view of Lowe et al. in further view of Tyagi (*Nature Biotechnol.* 14:303-308 (1996)). Specifically, the Office Action states that one of ordinary skill in the art would have been motivated to apply a molecular beacon probe for detection as taught by Tyagi et al. and that it would have been *prima facie* obvious to apply a molecular beacon probe for detection.

For the reasons discussed above, applicants submit that Laue and Lowe et al., alone or in combination, fail to disclose or suggest the primers and primer pairs of the presently claimed invention. Further, Tyagi et al. fails to remedy the deficiencies of Laue and Lowe et al. Tyagi et al. simply discloses the use of molecular beacon probes generally. Figure 1 provides the only specific probe and it bears no resemblance to the claimed probes of the present invention. Thus, similar to Laue and Lowe et al. with regard to the primer pairs of the present invention, applicants assert that Tyagi et al. fails to teach or suggest the specific oligonucleotide probes of the present invention. Simply describing the use of molecular beacons probes generally does not teach or suggest the specifically claimed probes of the present invention.

Accordingly, applicants submit that claim 15 is patentable over Laue in view of Lowe et al. in further view of Tyagi and respectfully request the withdrawal of this rejection.

E. Claims 19-21 stand rejected under 35 U.S.C. §103 as allegedly being unpatentable over Laue in view of Lowe et al. in further view of Compton (*Nature* 350:91-92 (1991)). Specifically, the Office Action states that one of ordinary skill in the art would have been motivated to apply a NASBA reaction for detection of SARS nucleic acid in a sample and that it would have been *prima facie* obvious to carry out a NASBA reaction and to make a kit including a NASBA reagent for detecting SARS nucleic acid in a sample.

For the reasons discussed above, applicants submit that Laue and Lowe et al., alone or in combination, fail to disclose or suggest the claimed primers and primer pairs of the present invention. Further, Compton fails to remedy the deficiencies of Laue and Lowe et al. Compton discloses the use of a standard NASBA reaction, but similar to Laue and Lowe et al., Compton fails to teach or suggest the specific primers, primer pairs and probes of the present invention and thus, fails to teach or suggest the use of the claimed primers, primer pairs and oligonucleotide probes as claimed herein in a NASBA reaction.

Accordingly, applicants submit that claims 19-21 are patentable over Laue in view of Lowe et al. in further view of Compton and respectfully request the withdrawal of this rejection.

The points and concerns raised in the Action having been addressed in full herein, it is respectfully submitted that this application is in condition for allowance, which action is respectfully requested. Should there be any remaining concerns, the Examiner is encouraged to contact the undersigned attorney by telephone to expedite the prosecution of this application.

The Commissioner is authorized to charge Deposit Account No. 50-0220 in the amount of $940.00 ($810.00 for a Request for Continued Examination and $130.00 for a one month extension of time). This amount is believed to be correct. However, the Commissioner is authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-0220.

Respectfully submitted,

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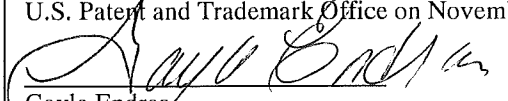

Gayle Endres